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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/072,301 | 02/08/2002 | Shaobing Hua | 25636-718 | 9688 |

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| EXAMINER | |
|---|---|
| PARKIN, JEFFREY S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 05/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/072,301 | HUA ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey S. Parkin, Ph.D. | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09152003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## Detailed Office Action

### *Status of the Claims*

Applicants' election of Group I (claims 1-26) without traverse in the communication dated 02 February, 2004, is acknowledged. Claims 27-35 were canceled without prejudice or disclaimer. Accordingly, claims 1-26 are currently under examination.

### *37 C.F.R. § 1.98*

The information disclosure statement filed 15 September, 2003, has been placed in the application file and the information referred to therein has been considered.

### *35 U.S.C. § 120*

If applicant desires priority under 35 U.S.C. § 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application. If applicant desires priority based upon a National Stage filing, this information should also be referenced in the first sentence of the specification (i.e., This application is a National Stage entry of International Application No. PCT/CCPY/NNNNN, filed , 199N).

### *Disclosure*

The disclosure is objected to because of the following

informalities: the priority information set forth on the first page of the specification is incomplete. Appropriate correction is required.

### *37 C.F.R. §s 1.821-1.825*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants are reminded that sequences appearing in the specification and/or **drawings** (e.g., **Figure 7**) must be identified by a sequence identifier (SEQ ID NO.:) in accordance with 37 C.F.R. § 1.821(d). Sequence identifiers for sequences appearing in the drawings may appear in the Brief Description of the Drawings. Applicant must provide appropriate amendments to the specification and/or drawings inserting the required sequence identifiers. Extensive amendments may necessitate the submission of a substitute specification.

### *35 U.S.C. § 112, Second Paragraph*

Claims 1-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are directed toward antibodies the bind to either the "N-terminus" or "loop 6" of the human chemokine receptor CCR5. This reference is vague and indefinite since it fails to set forth the precise binding specificity of the claimed antibodies. For instance, how does the skilled artisan ascertain at which point in the CCR5 molecule the antibody actually binds.

An antibody could recognize amino acids 1-5, 4-9, 10-15, etc., all of which are contained in or near the amino terminus of the protein of interest. The same problems exist with the reference to loop 6. At which point does the loop actually begin and end. Do the antibodies bind and recognize only amino acids in this region or is there some overlap with other regions? Perusal of the specification reveals that the claimed antibodies were actually directed against epitopes in a specific N-terminal fragment (amino acids 1-36 [SEQ ID NO.: 8]) and loop6/transmembrane domain-containing (amino acids 262-290 [SEQ ID NO.: 3]) fragment of CCR5. It is recommended that applicants amend the claim language to clearly set forth the binding specificity of the claimed antibodies (i.e., An isolated and purified antibody that binds to an epitope present in the amino terminus of a human CCR5 polypeptide consisting of SEQ ID NO.: 8 ...; An isolated and purified antibody that binds to an epitope present in the loop 6/transmembrane domain 7 region of a human CCR5 polypeptide consisting of SEQ ID NO.: 3 ...). Appropriate correction is required.

### *35 U.S.C. § 112, First Paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are broadly directed toward antibodies that bind to poorly defined regions in the hCCR5 protein. Perusal of the disclosure identifies four specific scFv

antibody molecules (clones 15.186.35, 15.150.11, 15.150.12, 15.150.24) that bind to the antigen of interest. Two of these antibodies displayed (clones 15.150.11 and 15.150.12) anti-HIV-1 activity. The other two antibodies were not tested. Thus, appropriately drafted claim language directed toward these specific embodiments would be acceptable (i.e., An isolated and purified anti-hCCR5 antibody consisting of SEQ ID NO.: 19). However, the claims do not support the full-breadth of the claimed invention, particularly where it is directed toward antibodies that just display one or two of the CDR domains.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

**1) The disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating antigen-antibody binding interactions in the context of the overall antibody configuration.** The claims encompass antibodies wherein only minimal structural requirements are provided. For instance, the only requirement may be that the antibody of interest contain a specific CDR2 or CDR3 domain. However, it is well-known in the art that antigen-antibody binding interactions require a complex three-dimensional configuration involving several complementarity determining regions

from both the heavy and light chains (Frazer and Capra, 1999). Thus, the skilled artisan would reasonably conclude that more than one single CDR is required for antigen-antibody binding interactions. However, without proper guidance, the skilled artisan has been extended an undue invitation to further experimentation to ascertain which other regions (i.e., FR, CDR, heavy chain, light chain) should be paired with the CDR of interest to achieve antigen binding.

**2) The state-of-the-art vis-à-vis the tertiary structure of antibodies is one of unpredictability.** Several factors influence the tertiary structure of the paratope, or antigen binding portion of an immunoglobulin. These include sequence composition and length variations in the CDRs, influence from adjacent framework regions, and posttranslational modifications such as glycosylation. Thus, the actual composition of the CDRs and FRs is critical for antibody affinity and avidity. The disclosure fails to provide any guidance concerning any of these issues.

**3) The disclosure fails to provide a sufficient number of working embodiments.** The disclosure identifies a total of four scFv antibodies that bind to either the amino terminus or loop 6/TMD 7 regions of hCCR5. Of these antibodies, only two displayed antiviral activity. The disclosure fails to provide sufficient guidance pertaining to acceptable amino acid changes within the CDRs and FRs that will retain the desired specificity and activity of the antibodies of interest. Considering the claim breadth and unpredictability of the prior art in predicting the effects of various sequence changes on the tertiary structure of antibodies, two scFv antibodies with the desired properties are insufficient to enable the full breadth of the claimed invention.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention in a manner commensurate in scope with the claims.

## *Correspondence*

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600.

Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

10 May, 2004